

Support for new Claim 67 can be found on page 30, lines 3-14.

Support for new Claim 68 can be found on page 30, lines 3-14.

Support for new Claim 69 can be found on page 30, lines 3-14.

Support for new Claim 70 can be found on page 28, line 4 through page 29, line 6.

Support for new Claim 71 can be found on page 30, lines 3-14.

Support for new Claim 72 can be found on page 28, line 4 through page 29, line 6.

Support for new Claim 73 can be found on page 28, line 4 through page 29, line 6.

Support for new Claim 74 can be found on page 28, line 4 through page 29, line 6.

Support for new Claim 75 can be found on page 28, line 4 through page 29, line 6.

#### Claim Rejections Maintained

The Examiner has maintained her rejection of claims 41 and 42 stating that they are not enabled by the specification. The Examiner concedes that the specification is enabling for methods based on the binding of ephrinB2 to ephB4. However, the Examiner reiterates that while the use of polypeptides consisting of the extracellular domain of a known protein is in fact art standard, the use of polypeptides comprising the any extracellular domain of any vein-specific cell surface protein, including those not yet described is not. The Examiner further states that the identification of one-artery specific molecule by another (Shutter et al., Genes and Dev., Vol. 14, pp. 1313-1318, 2000) does not indicate that the specification enabled the claimed invention at the time of filing. The Examiner also states that the instant specification does not provide sufficient guidance to enable one of skill in the art to predictably identify and thus use other artery- or vein-specific molecules. The Examiner also states that since ephrins and their receptors are widely distributed, the prior art encompassing their structural and functional requirements provides no guidance for identifying any other species of artery- or vein-specific molecule.

Respectfully, Applicants disagree. Applicants believe the specification is enabling for reasons previously outlined in the reply filed August 4, 2000. Additionally, it is the Examiner's opinion that since ephrins and their receptors are widely distributed, that the prior art encompassing their structural and functional requirements provides no guidance for identifying any other species of artery- or vein-specific molecule. It is art standard to classify newly isolated

genes into gene families by the structural and functional features exemplified in the prior art, such as ephrins and their receptors. It is also, art standard to use *in situ* hybridization and/or Northern blot hybridization, or immunohistochemistry to determine tissue distribution of newly identified genes. Therefore, using information provided in the specification and routine methods, one of ordinary skill can determine if newly identified members of the Ephrin family or their receptors are artery and vein-specific (respectively). Thus, undue experimentation is not required. In his article (Yancopoulos, G.D. et al. in *Cell*, Vol 93:5, May 29, 1998 at p. 661-2, in IDS filed March 22, 2000), Dr. Judah Folkman, a pioneer in the field of angiogenesis discussed the subject matter of this invention. In that article he states:

. . . ephrin-B2 marks future arterial but not venous endothelial cells, while one of the receptors for ephrin-B2 (i.e., Eph-B4) reciprocally marks the venous endothelium, at the earliest stages of capillary plexus, at a point when it had been assumed all endothelium was rather uniform in nature. These reciprocal expression patterns not only provide the earliest known markers distinguishing arterial and venous endothelium, but suggest that some sort of bidirectional signaling is occurring between these sets of cells.

Further, it should be noted that the Shutter *et al.* reference was cited to demonstrate the predictability of identifying other artery-specific molecules now possible due to the advances enabled by the instant invention, *not* for support of enablement as of the time of the invention.

The Examiner states that Claims 1-3, 5, 8-10, 41, and 42 are newly rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in such a way as to reasonably convey to one of skill in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. The Examiner also states that the Applicant has described one species, the EphB4/ephrin b2 system; [h]owever, applicant has not described the structural or functional characteristics sufficient to identify any other members of the genus described. The Examiner further states that Applicant has therefore described neither a representative number of members of the genus nor the relevant structural features of the genus, and that one of skill in the art would not be able to identify other members of the genus based on the instant disclosure.

Respectfully, Applicant disagrees. As outlined in the previous reply filed August 4, 2000, and above, the structural properties of Eph and Ephrin family proteins are detailed in the specification (page 6, lines 15-20, page 9, line 22 through page 10, line 11). Using information provided in the specification, the classification of additional family members would be routine in the art. The Applicants' invention enables one, for the first time, to identify artery- and vein-specific cells and assess the effect of soluble polypeptides on biological function. Because the Applicants' invention is now available, one skilled in the art using the Applicants' invention combined with routine skill can identify the genus of "artery-specific Ephrin family" and "vein-specific Eph family." To amend the claims to the particular EphrinB2 and EphB4 as suggested by the Examiner would unduly limit Applicants' claimed invention and invite those of skill in the art to easily design around Applicant's invention. The court has clearly stated that:

Depriving inventors of claims which adequately protect them and limiting them to claims which practically invite appropriation of the invention while avoiding infringement inevitably has the effect of suppressing disclosure (in re Angstadt and Griffin, 190 U.S.P.Q. 214, 219 (CCPA 1976)).

Thus, the Applicant respectfully request that the rejection of Claims 1-3, 5, 8-10, 41, and 42 be withdrawn.

The Examiner has maintained her rejection of Claims 1-3, 5 and 7 under 35 U.S.C. 112, second paragraph, is maintained. The Examiner states pages 21-23 detail methods of evaluating molecules that effect interactions between artery- and vein-specific molecules but at no point define the limitations of such an interaction, particularly distinct from "binding".

Applicants have amended claims 1 and 5 to delete "binding" and refer only to 'interaction'. Separate claims to 'binding' have been added to avoid confusion. Claims 1 and 5, as amended are believed to overcome Examiner's rejection.

The Examiner further states that Claims 12 and 43 are objected to for being dependent on a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims. In light of the above arguments which are incorporated by reference herein, these claims are believed to be patentable as written.

CONCLUSION

In view of the above amendments and remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned at (781) 861-6240.

Respectfully submitted,

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